DR. TONATIUH BARRIENTOS-GUTIÉRREZ (Orcid ID : 0000-0002-0826-9106)
DR. SIMÓN BARQUERA (Orcid ID : 0000-0003-1854-4615)

Article type : Original Article

The association between obesity, type 2 diabetes, and hypertension with severe COVID-19 on admission among Mexicans

Edgar Denova-Gutiérrez[1], Hugo Lopez-Gatell[2], Jose L. Alomia-Zegarra[3], Ruy López-Ridaura[4], Christian A. Zaragoza-Jimenez[3], Dwigth D. Dyer-Leal[5], Ricardo Cortés-Alcala[5], Tania Villa-Reyes[3], Rosaura Gutiérrez-Vargas[3], Kathia Rodríguez-González[3], Carlos Escondrillas-Maya[3], Tonatiuh Barrientos-Gutiérrez[6], Juan A. Rivera[1], Simón Barquera[1]

[1] Centro de Investigación en Nutrición y Salud, Instituto Nacional de Salud Pública. Cuernavaca, Morelos, México.
[2] Subsecretario de Prevención y Promoción de la Salud, Secretaria de Salud. Ciudad de México, México.
[3] Direccion General de Epidemiologia, Secretaria de Salud, Ciudad de México, México.
[4] Dirección General del Centro Nacional de Programas Preventivos y Control de Enfermedades, Secretaria de Salud. Ciudad de México, México.
[5] Dirección General de Promoción de La Salud, Secretaria de Salud. Ciudad de México, México.
[6] Centro de Investigación en Salud Poblacional, Instituto Nacional de Salud Pública. Cuernavaca, Morelos, México.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/oby.22946

Key words: COVID-19; Obesity; Type 2 Diabetes; Hypertension, Mexican population

Running title: Obesity, chronic diseases, and COVID-19

Corresponding author: Simón Barquera. Centro de Investigación en Nutrición y Salud, Instituto Nacional de Salud Pública. Av. Universidad No. 655, Col. Santa María Ahuacatitlán, C.P. 62100, Cuernavaca, México. E-mail: sbarquera@insp.mx

Funding: None.

Disclosures: The authors declared no conflict of interest.

Authors' contribution: SB, HL-G, TB-G, JAR and ED-G came up with the idea and analysis plan for the present study; RC-A, JA-Z, CZ-J, DD-L, TV-R, RG-V, KR-G, CE-M, and HL-G had full access to all data and take responsibility for the integrity of the data; ED-G and SB conducted the data analysis. EDG and SB contributed to writing the first version of the manuscript. ED-G, RC-A, JA-Z, CZ-J, DD-L, HL-G, TB-G, JAR and SB critically revised the manuscript. All authors reviewed and approved the final version.

Word count: 2149 words

What is already known about this subject?

Previous studies have highlighted the relationship between obesity and higher risk of infectious diseases. Some of these studies have reported the association between obesity and the risk of a severe form of COVID-19.

What are the new findings in your manuscript?

We analyzed data from 3,844 patients who tested positive for COVID-19. After adjusting for age, sex, smoking status, history of chronic diseases (hypertension, diabetes, cardiovascular disease, chronic kidney disease, immunosuppression) and drug treatment, people with obesity showed a 1.43-fold higher odds of developing severe COVID-19 on admission compared to patients without obesity. Additionally, this is the first study that evaluates the association between obesity, diabetes, and hypertension with severe COVID-19 on admission among the Mexican population.

How might your results change the direction of research or the focus of clinical practice?

If causality exists between obesity, diabetes, hypertension, and COVID-19, it will help the health sector better target vulnerable populations and assess the risk of deterioration.

Abstract

Objective: To explore the association between obesity, type 2 diabetes, hypertension, and severe COVID-19 on admission.

Methods: In the present study, a total of 23,593 patient samples were evaluated by a laboratory from the Mexican Institute of Epidemiological Diagnosis and Reference (InDRE, for its acronym in Spanish). Of these: 18,443 were negative for COVID-19, 3,844 were positive for COVID-19, and 1,306 were positive for other respiratory viruses. Severe types of respiratory disease were defined by

the presence of pneumonia and other organ failure that requires intensive care. Multivariable logistic regression models were used to explore factors associated with severe COVID-19 on admission.
Results: Patients who tested positive for COVID-19 had a higher proportion of obesity (17.4%), diabetes (14.5%), and hypertension (18.9%), compared to those without a confirmed diagnosis. Compared to non-obese patients, those with obesity showed a 1.43-fold higher odds of developing severe COVID-19 on admission, while subjects with diabetes and hypertension showed a 1.87-fold and 1.77-fold higher odds of developing severe COVID-19 on admission, respectively.
Conclusion: Obesity, diabetes, and hypertension were significantly associated with severe COVID-19 on admission and the association of obesity was stronger in patients < 50 y.

Introduction

The new coronavirus 2019 epidemic (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has spread worldwide and poses a critical threat to public health around the world. Rapidly communicating information related to the virus is a current priority for disease prevention and control (1-3).

Obesity has been linked with a greater risk of inflammation and other chronic conditions (4,5). In addition, previous studies have highlighted the relationship between obesity, diabetes, and a higher risk of infectious diseases (6,7). For example, obesity has long been recognized as a risk factor for increased morbidity and mortality associated with the influenza A (H1N1) infection (8). This is a major challenge in countries like Mexico where obesity prevalence (40.1% in women and 26.6% in men) ranks as one of the highest in the world and has continued to increase during the last three decades, particularly in low- and middle-income groups (9).

Previous reports (1,3,10,11) suggest that people over age 60 and those with obesity have a higher risk of severe COVID-19 complications. For that reason, understanding and quantifying this risk is key to enabling patients, care givers, and healthcare professionals to make informed decisions about ways to manage risk in patients with obesity, type 2 diabetes or hypertension during the COVID-19 pandemic. Thus, the present study hypothesized that patients with obesity, diabetes, and hypertension would experience greater odds of developing severe COVID-19 on admission. If so, this might provide insights for Mexican health authorities and other middle-income or developing countries with a high prevalence of obesity.

Methods

Design and study participants

In Mexico, COVID-19 reporting follows two general procedures. Hospital surveillance keeps track of all deaths and hospitalizations, providing a census of confirmed COVID-19 cases. In addition, sentinel surveillance is carried out through a system of selected health units that monitor respiratory diseases (USMER, by its Spanish acronym) (Figure 1). USMERs include medical units from the first, second, or third level of care that have enough material and human resources to follow strict clinical evaluation protocols to identify respiratory disease, as well as the infrastructure to produce timely and complete epidemiological reports (12). A total of 475 USMER units are distributed across the country and every Mexican state has at least one reporting unit. Although sentinel units were not selected randomly, sentinel surveillance is the most effective way to collect good quality and timely data on respiratory diseases in Mexico. The spectrum of severity of COVID-19 infections varies greatly. In this sense, the sentinel surveillance system focuses on mild manifestations of mostly community cases, while severe patients that require hospital treatment are documented by hospital-based surveillance.

In the present study, the information collected from National Epidemiological Surveillance System (SINAVE, SISVER, for its acronym in Spanish) started on February 27, 2020, when the first case of COVID-19 in Mexico was confirmed, and ended-on April 10, 2020. A total of 33,893 subjects were included in the Epidemiological Surveillance System for viral respiratory disease (SISVER, for its acronym in Spanish) platform (**Figure 1**). Of these, 23,593 patient samples were tested for SARS-

CoV-2 by the laboratory from the Mexican Institute of Epidemiological Diagnosis and Reference (InDRE, for its acronym in Spanish) or by any other public or private laboratory in Mexico. Of the 23,593 samples for which results were available, 18,443 were negative for COVID-19, 3,844 were positive for COVID-19, and 1,306 were positive for other respiratory viruses such as H1N1.

For the initial analysis, we only included those who were negative or positive for COVID-19 and who had complete information. In the final analysis, only those who were positive for COVID-19 were included.

Data collection

Confirmation of COVID-19

This study utilized the information collected by every state through first, second, and third level medical care units, which evaluate suspected cases of viral respiratory disease, based on an operational definition (person of any age who in the past 7 days has had at least two of the following signs and symptoms: cough, fever, or headache, accompanied by at least one of the following signs or symptoms: dyspnea, arthralgia, myalgia, odynophagia, rhinorrhea, conjunctivitis or chest pain.)

Among these suspected cases, two protocols were followed: a) SARS-CoV-2 testing for suspected COVID-19 cases with severe acute respiratory infection with signs of breathing difficulty, and b) for all other suspected cases, sentinel surveillance was utilized (13). This definition was approved by the National Epidemiological Surveillance Committee (CONAVE, by its Spanish acronym) (14). Once collected, this information was uploaded to the SISVER online platform.

The presence of SARS-CoV-2 was diagnosed by the real-Time Reverse Transcription Polymerase Chain Reaction method, based on the Berlin protocol (15,16). Only laboratory-confirmed cases were included in the final analysis.

A consent disclaimer was obtained for the purposes of this study. This cross-sectional study was performed in line with the Strengthening the Reporting of Observational Studies in Epidemiology statement.

Outcome assessment

For the present study, the primary outcome was a severe form of COVID-19. All patients were classified into severe and mild respiratory disease based on results from a clinical examination and their symptoms. Patients who only had symptoms like cough, expectoration, and other upper respiratory tract symptoms were classified as non-severe. Severe types of respiratory disease on admission were defined by the presence of pneumonia and other organ failure that requires monitoring and treatment in the intensive care unit (ICU).

Additionally, information on the date of onset of symptoms and hospital admission are available for all cases, as well as the status of treatment (outpatient or hospitalized), information on the diagnosis of pneumonia, and admission to the ICU (13).

Assessment of covariates

In most cases (68% approximately), information on obesity, type 2 diabetes, and hypertension was obtained by the attending physician by self-report from the patient. For the rest (32% approximately), information was obtained by self-report and was corroborated with medical records.

The attending physician collected epidemiological, other clinical information (presence of comorbidities), laboratory, and treatment, as well as demographic characteristics (e.g., age, sex), and tobacco consumption, using a standardized questionnaire. This information was subsequently recorded on the SISVER online platform.

Statistical Analyses

Descriptive analyses of the main characteristics of interest were performed. Categorical variables were described as percentages and continuous variables as mean and standard deviation. Means for continuous variables were compared using independent group t-tests. Comparisons for categorical variables were done using the chi square test or the Fisher exact test. Multivariable logistic regression models (one model for each condition) were used to explore obesity, diabetes and hypertension with a severe COVID-19 on admission; odds ratios (OR) and 95% confidence intervals (95% CIs) were estimated.

To assess the possible effect of modification, we explored stratified analyses by age (two categories: $<=$ 50 years vs $\geq$ 51 years). We tested the significance of the interaction with a likelihood ratio test by comparing a model with the main effect variable and the interaction terms with a reduced model with only the main effects.

All *P* values presented are two sided; $P < 0.05$ was considered statistically significant. The statistical analyses were performed using the STATA statistical software package, version 13.0 (Stata Corp. LP: College Station, TX).

Results

When comparing the patients who tested positive for COVID-19 to those who tested negative, we observed that the positive patients had a mean age of 45.4 years and a higher proportion of them were over age 60 (19.4%). Additionally, patients who were positive for COVID-19 had a higher proportion of obesity (17.4%), diabetes (14.5%), and hypertension (18.9%), compared to those without a confirmed diagnosis (**Table 1**).

The characteristics of patients who tested positive for COVID-19 were stratified by obesity condition (**Table 2**). Of them, 17.4% had obesity and 82.6% did not have obesity. We observed a higher number of older patients with obesity than in the patients without obesity (23.0% vs 18.7%, P<0.001). Patients with obesity also had a higher prevalence of other chronic diseases, such as diabetes (29.3%), hypertension (36.1%), cardiovascular disease (5.9%), and chronic kidney disease (2.3%). Patients with obesity were more likely to have symptoms such as fever (P<0.001), cough (P = 0.005) and dyspnea (P<0.001), compared to patients without obesity. Finally, a higher proportion of patients with obesity required ICU support and invasive medical ventilation.

Table 3 shows that after adjusting for age, sex, smoking status, history of chronic diseases (cardiovascular disease, chronic kidney disease, immunosuppression), place of care, USMER, and drug treatment, patients with obesity showed a 1.43-fold higher odds of developing severe COVID-19 on admission compared to patients without obesity. Also, patients with diabetes had a 1.87-fold higher odds of severe COVID-19 on admission compared to those without diabetes. Finally, patients with hypertension had a 1.77-fold higher odds of severe COVID-19 on admission compared to those without hypertension.

We examined the statistical interaction between age (< 50y vs >= 50 y) and the presence of obesity on their odds for severe COVID-19 on admission. The reference group did not have obesity and were < 50 y of age. Relative to the reference group, the odds ratio of the group with obesity (also < 50y) was 1.88 (95% CI: 1.26, 2.55). The odds ratio for the group without obesity > 50y was 1.51 (95% CI: 1.03, 2.20) versus 1.67 for the group with obesity >50y (95% CI: 1.01, 2.63) (Figure 2) (P for interaction 0.03). Additionally, we evaluated the possible interaction between hypertension and diabetes with age. However, these interactions were not statistically significant.

Finally, we performed a sensitivity analysis according to the origin of the patients (USMER vs non-USMER). Although the patients from USMER had higher odds of severe COVID-19 on admission, they were not statistically different from those who came from non-USMER institutions (data not shown).

Discussion

To our knowledge, this is the first study that evaluates the association between obesity, diabetes, and hypertension with severe COVID-19 on admission among the Mexican population. Our data suggests that these conditions are associated with severe COVID-19 on admission.

We observed that among patients with COVID-19, 17.4% had obesity, 14.5% had diabetes, 18.9% had hypertension, and 2.8% had cardiovascular disease. Similar to our data, recent studies from China claim that hypertension was prevalent in approximately 17% of the patients with COVID-19, while diabetes, cardiovascular diseases, and chronic kidney disease were present in 8%, 5%, and 2% of the cases, respectively (17-21).

Our analysis found that compared to patients without obesity, patients with obesity had 1.42 times the odds of developing severe COVID-19 on admission. A recent study by Xu et al. (3) found a similar association between higher body mass index and greater odds of developing severe disease. Compared to patients with normal weight, patients with obesity showed 2.42-fold higher odds (95% CI: 1.42, 8.27; $P = 0.004$) of developing a severe form of COVID-19 (3). Additionally, recent studies conducted by Kalligeros et al. (11), and Simmonet et al. (10) found that obesity is a risk factor for severe COVID-19.

People living with diabetes have been considered at higher risk of infections (17), which is consistent with our finding of 1.87-fold higher odds of developing severe COVID-19 on admission in patients with diabetes. However, a recent systematic review and meta-analysis found that the odds of developing a severe form of COVID-19 in people living with diabetes was not statistically significant (OR = 2.07; 95% CI: 0.89, 4.82) (18).

Specific comorbidities associated with an increased risk of infection and severity of COVID have been reported. In this sense, one of the most commonly reported comorbidities was hypertension (22,23). However, there is still no evidence that hypertension is related to the COVID-19 results. Our data suggest that patients with hypertension had 77% greater odds of developing severe COVID-19 on admission, compared to patients without hypertension.

To our knowledge, there are no previous studies in Mexico evaluating the joint effect of age and the presence of obesity. Our findings suggest that patients with obesity aged <= 50 years were 1.88 times more likely to develop severe COVID-19 on admission, while patients with obesity aged >= 50 years were 1.67 times more likely to develop severe COVID-19 on admission, compared to patients without obesity aged <= 50 years. A study found that patients with obesity under age 60 were more likely to be admitted to acute and critical care (24).

Despite the fact that the exact mechanisms by which obesity increases the severity of COVID-19 have not been clearly described, multiple mechanisms may play a role. Patients with obesity have an affected respiratory physiology, involving decreased functional residual capacity and expiratory reserve volume, as well as hypoxemia and ventilation/perfusion abnormalities (25). Obesity and other chronic conditions, like diabetes, might be significant in the pathogenesis of COVID-19 infection. The immune system, which plays an important role in the pathogenesis of COVID-19, is also a crucial element in obesity-induced adipose tissue inflammation. This inflammation of adipose tissue has been linked to metabolic dysfunction, which in turn has been associated with dyslipidemia, type 2 diabetes, hypertension, and cardiovascular disease (26,27). In addition, a number of possible mechanisms have been proposed for the increased risk of severe clinical outcomes in COVID-19 for people living with diabetes, including elevated plasmin levels, imbalance of angiotensin converting enzyme 2 and cytokines, reduced viral clearance, insulin resistance, and increased inflammatory markers (26-29). Also, obesity and diabetes have been linked with impaired immune responses to viral and bacterial infections (6,7,19) like influenza A; therefore, by analogy, obesity may play an important role in COVID-19 transmission and the severity of disease. For example, in the case of influenza A, obesity increases the duration of virus shedding; symptomatic patients with obesity shed the virus 42% longer than adults without obesity (26,30). Moreover, diabetes was proven to be an important risk factor for mortality in patients infected with influenza A (19).

The present study has some important limitations. First, this is an administrative dataset which was developed to monitor the epidemic and not specifically designed to follow-up patients; thus, information is only available at the moment in which people were registered in the system. Therefore, no information is available regarding the severity of the patients later on. Second, despite the fact that the data is from patients from all over Mexico, patients who were asymptomatic or treated at home are not part of the data, so our study represents only the more severe cases of COVID-19, and the results cannot be extrapolated to non-severe COVID-19 cases. Furthermore, since sentinel units were not randomly selected, our findings are not likely to be representative of the entire population. Third, in most cases, obesity was defined by self-report. In this sense, a classification error cannot be ruled out, and this would bias the observed associations towards the null value. In addition, self-report of obesity may be the reason behind the low obesity prevalence in the present study, compared to the prevalence observed at the national level. An additional potential source of bias is the origin of the patients' information (USMER vs non-USMER); however, the separate sensitivity analyses of patients according to their origin found consistent results between groups. Notwithstanding the limitations, this study has some strengths. First, comparative studies between obesity and chronic conditions associated with severe disease caused by SARS-CoV-2 are scarce; therefore, our results may help identify these associations. Second, the sample size permitted a multivariable analysis, consequently reducing the possibility of confounding factors. Third, although it is probable that our findings are not representative of the entire population, our study contains nationwide data.

In conclusion, obesity, diabetes and hypertension—important public health problems in Mexico—were significantly associated with severe COVID-19 on admission. In addition, the association of obesity was stronger in patients < 50 y. As previously suggested (26), this pandemic has shown us that more must be done to combat and prevent obesity in our societies in order to reduce the burden of chronic diseases and adverse outcomes to viral pandemics. Finally, our data suggest the need for studies that evaluate the mechanisms associated with increased severity of COVID-19 in patients with obesity, as well as the need for prevention strategies for these patients.

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Aknowledments

We thank Mariel White for her support in proofreading. Also, we thank Ana Estudillo for her time and support during the present analysis.

Data sharing

The data that support the findings of this study are available from the corresponding author on reasonable request. A proposal with a detailed description of study objectives and a statistical analysis plan will be needed to evaluate requests for our data. The corresponding author will decide based on these materials.

Table 1. Characteristics of patients analyzed by the laboratory of the Mexican Institute of Epidemiological Diagnosis and Reference.

Characteristics	COVID-19 n = 3844	Negative to COVID-19 n = 18443	P-value
Age, years[1]	45.4 ± 15.8	38.8 ± 17.5	<0.001
Age, %			
< 19 years	2.6	8.9	
20 to 59 years	78.0	78.5	<0.001
> 60 years	19.4	12.6	
Sex, %			
Women	42.0	54.5	<0.001
Men	58.0	45.5	
Smoking status, %			
Yes	9.5	10.5	0.06
Chronic conditions			
Obesity, %	17.4	12.8	<0.001
Diabetes, %	14.5	9.6	<0.001
Hypertension, %	18.9	14.4	<0.001
Cardiovascular disease, %	2.8	3.3	0.09
Chronic kidney disease, %	1.7	2.1	0.07
Immunosuppression	1.0	1.0	0.55
Initial symptoms			
Fever	79.5	66.3	<0.001
Cough	86.2	83.5	<0.001
Sore throat	45.0	49.8	<0.001
Nasal congestion	41.0	46.2	<0.001
Dyspnea	37.2	27.6	<0.001
Headache	78.9	76.9	0.02
Muscle pain	64.7	52.9	<0.001
Arthralgia	58.3	48.0	<0.001
Diarrhea	20.7	16.0	<0.001
Vomiting	7.7	7.6	0.17
Abdominal pain	15.4	14.2	0.07

Conjunctivitis	14.9	13.9	0.09
Treatment, %			
Antiviral treatment, %			
Yes	19.2	15.7	<0.001
Need ICU care, %			
Yes	12.7	6.9	<0.001
Invasive mechanical ventilation, %			
Yes	12.1	5.7	<0.01

[1] Mean ± standard deviation.

[2] Instituto Mexicano del Seguro Social (IMSS, by its Spanish acronym).

[3] Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE, by its Spanish acronym).

[4] Secretaria de Salud (SSA, by its Spanish acronym).

Table 2. Characteristics of patients with COVID-19 according to the obesity condition.

Characteristics	Total n = 3844	Non-obese n = 3176	Obese n = 668	P-value
Age, years[1]	45.4 ± 15.8	44.9 ± 16.1	48.2 ± 14.0	<0.001
Age, %				
＜ 19 years	2.6	2.9	0.9	
20 to 59 years	78.0	78.4	76.1	0.001
> 60 years	19.4	18.7	23.0	
Sex, %				
Women	42.0	42.2	41.8	0.85
Men	58.0	57.8	58.2	
Smoking status, %				

Yes	9.5	8.5	13.9	<0.001
Chronic conditions				
Diabetes, %	17.4	11.3	29.3	<0.001
Hypertension, %	14.5	15.3	36.1	<0.001
Cardiovascular disease, %	18.9	2.1	5.9	<0.001
Chronic kidney disease, %	2.8	1.6	2.3	0.27
Immunosuppression	1.0	0.85	1.1	0.55
Initial symptoms				
Fever	79.5	78.0	86.2	<0.001
Cough	86.2	85.5	89.7	0.005
Sore throat	45.0	44.4	47.5	0.03
Nasal congestion	41.0	40.6	42.8	0.03
Dyspnea	37.2	34.2	51.2	<0.001
Headache	78.9	78.9	78.7	0.76
Muscle pain	64.7	63.8	68.7	0.01
Arthralgia	58.3	57.1	64.1	<0.001
Diarrhea	20.7	18.9	29.1	<0.001
Vomiting	7.7	7.2	11.2	<0.001
Abdominal pain	15.4	14.5	21.1	<0.001
Conjunctivitis	14.9	14.4	17.4	0.02
Treatment, %				
Antiviral treatment, %				
Yes	19.2	18.7	21.7	<0.001
Need ICU care, %				
Yes	12.7	3.5	6.7	<0.001
Invasive mechanical ventilation, %				
Yes	12.1	3.2	6.3	<0.01
Disease progression, %				
Home monitoring	15.5	16.1	12.3	
In treatment	56.6	58.4	47.2	
Medical release	2.7	2.8	2.6	<0.001
Severe case	16.4	15.1	22.9	
Death	8.8	7.5	15.0	

[1] Mean ± standard deviation.

[2] Instituto Mexicano del Seguro Social (IMSS, by its Spanish acronym).

[3] Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE, by its Spanish acronym).

[4] Secretaria de Salud (SSA, by its Spanish acronym).

Table 3. Association between obesity, diabetes and hypertension with severe COVID-19 on admission.

Variable	Age adjusted model		Multivariate model	
	OR	95% CI	OR	95% CI
		Obesity[1]		
Total				
Non-obese	1.0	--	1.0	--
Obese	1.76	1.39, 2.23	1.43	1.11, 1.83
Men				
Non-obese	1.0	--	1.0	--
Obese	2.25	1.55, 3.25	1.75	1.15, 2.57
Women				
Non-obese	1.0	--	1.0	--
Obese	1.52	1.12, 2.08	1.30	1.03, 1.81
		Diabetes[2]		
Total				
Non-diabetes	1.0	--	1.0	--
Diabetes	3.53	2.78, 4.48	1.87	1.41, 4.26
Men				
Non-diabetes	1.0	--	1.0	--
Diabetes	2.61	1.73, 3.81	1.87	1.19, 2.94
Women				
Non-diabetes	1.0	--	1.0	--
Diabetes	2.10	1.52, 2.89	1.86	1.30, 2.64
		Hypertension[3]		
Total				
Non-hypertension	1.0	--	1.0	--
Hypertension	2.12	1.68, 2.68	1.77	1.37, 2.29

Men				
Non-hypertension	1.0	--	1.0	--
Hypertension	2.85	1.96, 4.15	2.33	1.56, 3.49
Women				
Non-hypertension	1.0	--	1.0	--
Hypertension	1.73	1.28, 2.34	1.50	1.07, 2.08

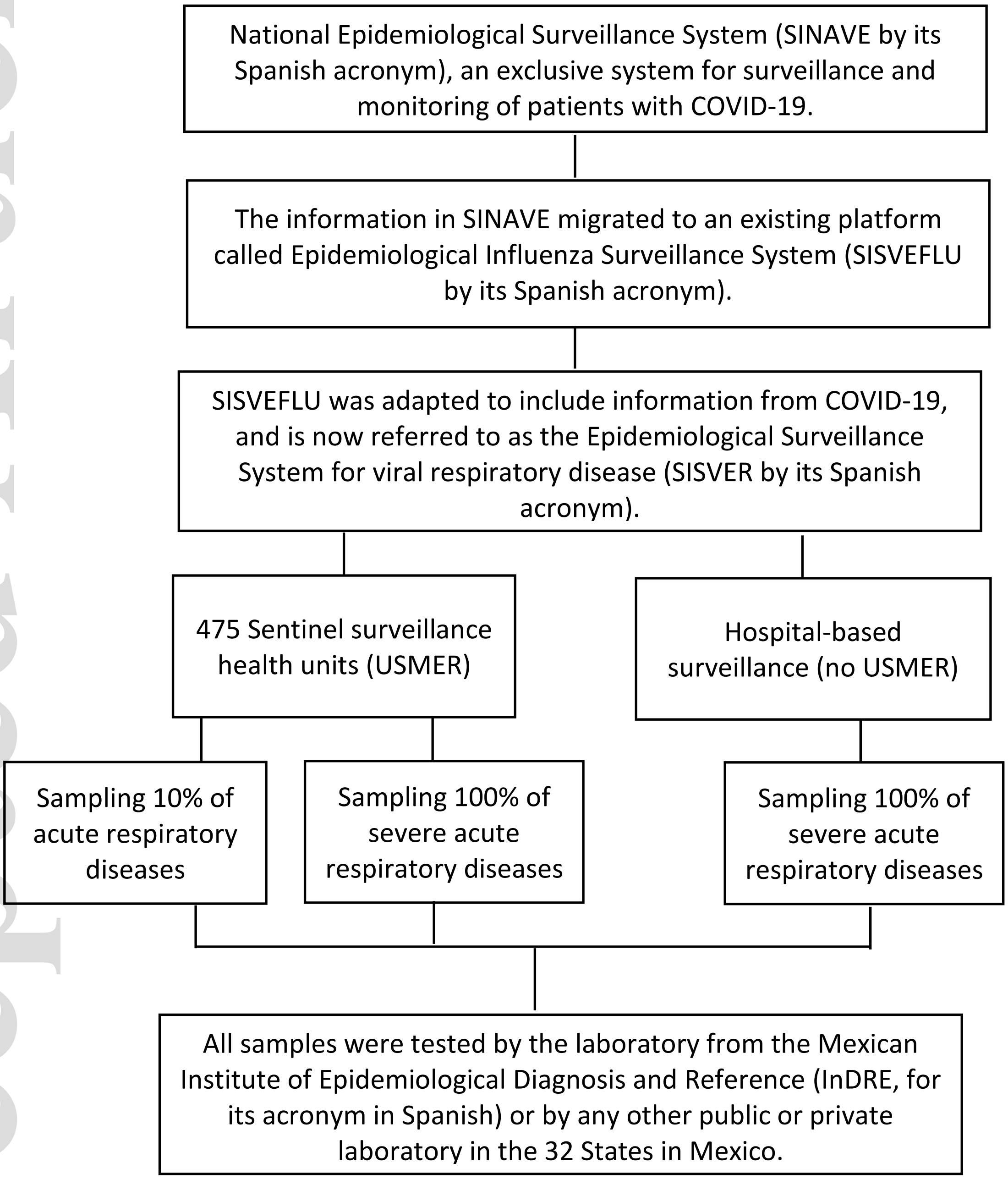
[1] Adjusted for age, sex, smoking status, history of chronic diseases (diabetes, hypertension, cardiovascular disease, chronic kidney disease, immunosuppression), place of care, USMER[2], and drug treatment.

[2] Adjusted for age, sex, smoking status, obesity, history of chronic diseases (hypertension, cardiovascular disease, chronic kidney disease, immunosuppression), place of care, USMER[4], and drug treatment.

[3] Adjusted for age, sex, smoking status, obesity, history of chronic diseases (diabetes, cardiovascular disease, chronic kidney disease, immunosuppression), place of care, USMER[2], and drug treatment.

[4] USMER: Health units of the sentinel surveillance system

Figure 1. Flow chart of the Mexican National Epidemiological Surveillance System for viral respiratory diseases.



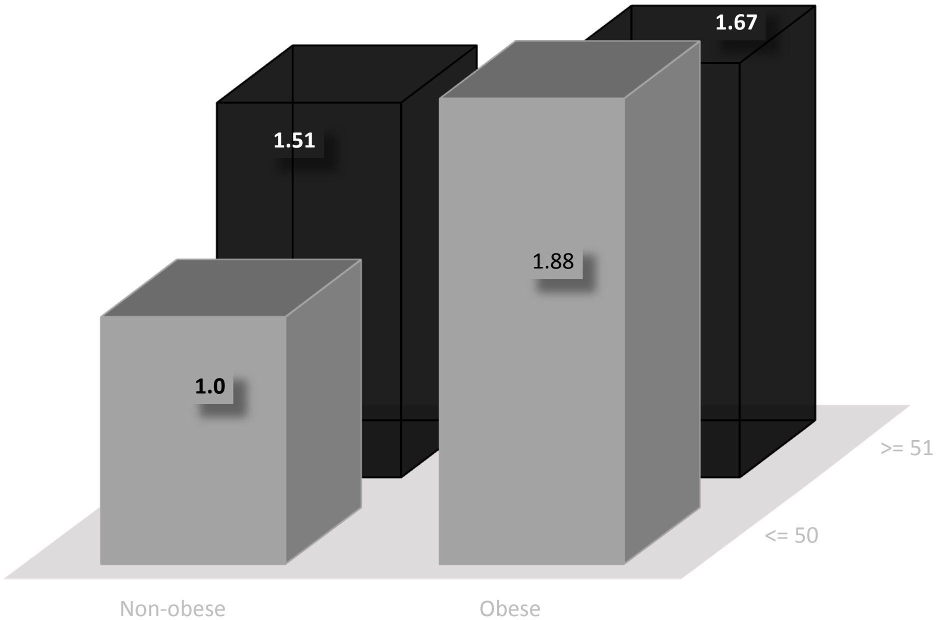


Figure 2. Joint association of Obesity and age (<= 50 years and >= 51 years) with severe COVID-19 on admission in the Mexican population.

Reference group for comparisons were subjects without obesity and <= 50 years. Odds ratio were adjusted for: age (years), sex, smoking status, history of chronic diseases (hypertension, diabetes, cardiovascular disease, chronic kidney disease, immunosuppression), place of care, USMER[1], date of symptoms onset and drug treatment

[1] USMER: Health units of the sentinel surveillance system